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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
BRANNOCK, M	
ART UNIT	PAPER NUMBER
1646	14

DATE MAILED: 10/22/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/389,835	Ruoho et al.
Examiner	**Art Unit**
Michael Brannock, Ph.D.	1646

-- The MAILING DATE of this communication appears on th cov r she t with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 6, 2001*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-14* is/are pending in the applica

4a) Of the above, claim(s) *13 and 14* is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-12* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Status of Application: Claims and Amendments

1. Claims 1-14 are pending. Applicant's election with traverse of Group I, claims 1-12 in Paper 13, 8/10/01 is acknowledged. The traversal is on the grounds that a search of Groups I and II would not be a serious burden on the examiner. This is not found persuasive for the following reasons:

Under MPEP § 803, there are two criteria for a proper requirement for restriction between patentably distinct inventions:

(A) The inventions must be independent (see MPEP § 8702.01, 806.04, 808.01) **or** distinct as claimed (see MPEP § 806.05- §806.05(I)): and

(B) There must be a serious burden on the examiner if restriction is required (see MPEP § 803.02, § 806.04(a)- 806.04(I), § 808.01(a), and § 808.02).

Consistent with current patent practice, a serious search burden may be established by (A) separate classification thereof: (B) a separate status in the art when they are classifiable together: (C) a different field of search. These criteria were met in the above restriction. Further, a search is directed not only to art which would be anticipatory, but also to art that would render the invention obvious. In the instant case, although a search of the polypeptides and polynucleotides of Group I would overlap a search of the methods of Group II, the two searches would not be coextensive, because the polynucleotides and polypeptides of Group I may have been used in many other methods besides the method of group II that would not necessarily appear in a

disclosure of the methods of Group II, e.g. for mapping the topology of membrane proteins or for the production/purification of proteolytic fragments of the chimeric proteins, see page 397 of Popot *et al.*, *Current Opinion in Biotechnology* 6:394-402, 1999. Thus, Groups I and II require divergent searches, and to search both inventions would be burdensome. Therefore, the restriction is maintained and made final.

Claim Objections

2. Claim 11 is objected to because of the following informalities: it appears that the word "of" is missing between the words "step" and "culturing" in line 3 of the claim. Additionally it appears that the word "a" is missing between "having" and "bacteriorhodopsin" in line 7. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 6-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims require that a portion of bacteriorhodopsin is replaced with the structurally analogous region of a G-protein coupled receptor protein. The phrase "structurally analogous region" renders the claims indefinite because the specification does define not set forth a definition of this phrase that the skilled artisan could use to determine what is and what is not encompassed by the claims, see page 10. While it is acknowledged that bacteriorhodopsin is famous as a template to construct three dimensional models of G-protein coupled receptors (GPCRs), see Hoflack *et al., Trends in Pharm. Sci.* 15:7-9, 1994, especially col. 1 of page 7, the art is equivocal as to the precise structural relationships between bacteriorhodopsin and G-protein coupled receptors. For example, Pardo *et al., PNAS* 89:4009-4012, 1992 teach that the transmembrane regions, in particular, of bacteriorhodopsin and G-protein coupled receptors, do not correspond to each other. Further, Sohlemann *et al. Naunyn Schmiedebergs Archives of Pharm.* 355(2)150-160, 1997 acknowledge that available structural data suggest that bacteriorhodopsin and rhodopsin (a GPCR) share overall topology, however there are clear differences in the packing of the helices. In the present state it is not clear what types of relationship[s] exist between bacteriorhodopsins and GPCRs", see page 151 first col. Thus, one of skill in the art could not rely on the prior art to know, unambiguously, which structures are

analogous between bacteriorhodopsin and GPCRs, as would be required to establish the bounds of the claims.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 4 and 5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for chimeric bacteriorhodopsin/GPCR chimeras capable of activating GTP-GDP exchange on a G-protein in vitro wherein the GPCR is bovine rhodopsin or another opsin, does not reasonably provide enablement for other G-protein coupled receptors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The specification indicates that chimeras of bacteriorhodopsin and bovine rhodopsins can be constructed that activate the rhodopsin specific G-protein transducin. One of skill in the art would expect that these chimeras would be capable of activating transducin because bacteriorhodopsin and the visual opsins (e.g. rhodopsin, and the color opsins) share the unique structural and functional mechanism of light activation via isomerization of covalently bound 11-cis-retinal. No other GPCRs are known to function in this way and the specification has not taught how to make a loop III from any other of the structurally and functionally divergent GPCRs (e.g. serotonin, metabotrophic glutamate receptors) function in the context of

bacteriorhodopsin. The claims encompass these GPCRs yet there is no teachings other than an invitation to one of skill in the art to begin a research program to randomly generate and, through trial and error experimentation, try to find other GPCR loop IIIs that will function as required by the claims. It is unclear from the specification exactly how many of the rhodopsin/bacteriorhodopsin constructs actually worked as claimed, however it is clear that many did not (see page 10, middle paragraph, wherein it was stated that "some but not all of the chimeras were found to enhance GTP-GDP exchange"). Thus, one would expect a great deal of variation amongst the rhodopsin/bacteriorhodopsin chimeras; reasonable extrapolation of this data would indicate that other non-rhodopsin GPCRs would be even more problematic, if indeed any can be found to work.

Therefore, due to the large quantity of experimentation necessary to generate the infinite number of chimeras recited in the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which non-rhodopsin GPCRs would work, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the divergent nature of function between rhodopsin and other GPCRS, and the breadth of the claims which fail to recite GPCRs that would be expected to function as claimed, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 11 and 12are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No: 5641650.

U.S. Patent No: 5641650 discloses a chimeric fusion protein comprising a bacteriorhodopsin protein amino acid sequence (signal sequence or C-terminal, see col 2) which at least a portion of the protein (e.g. the remaining parts of the protein) are replaced with the structurally analogous region of a G-protein receptor (e.g. serotonin receptor, see col 8). U.S. Patent No: 5641650 further disclose methods of producing the protein comprising culturing an archaebaterium comprising the construct encoding the protein connected to a promoter sequence functional in the archaebacterium under suitable condition and for a period time sufficient to allow expression of the chimeric fusion protein and then partially purifying the chimeric fusion protein, see cols 11 and 12.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-3, 6-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Popot *et al.*, *Current Opinion in Biotechnology* 6:394-402, 1999 in view of Hoflack *et al., Trends in Pharm. Sci.* 15:7-9, 1994.

Popot *et al.* teach that that chimeric constructs of bacteriorhodopsin and of G-protein receptors can be made for the purposes of functional and structural investigations (pg 396 col 1); that bacteriorhodopsin "can be used as a 'benchtop' on which to arrange engineered loops that are designed to form binding or catalytic sites (pg 397 col. 2), and that a wealth of data indicates that most of the six loops connecting the transmembrane helices in bacteriorhodopsin can be tampered with to large extents and at least three of them can be cut without preventing refoloding of the proteins (e.g. cytoplasmic loop III, reference 61) (pg 397 col. 2); and that the cytoplasmic loops of rhodopsin are tolerant to modification (pg 397 col. 2). Further, it is old and well established in the art that bacteriorhodopsin is famous as a template to construct three dimensional models of G-protein coupled receptors (GPCRs), see Hoflack *et al., Trends in Pharm. Sci.* 15:7-9, 1994, especially col. 1 of page 7. Further, the use of archaebacterium for

recombinant expression of bacteriorhodopsin chimeras is old and well established in the art, as disclosed by Popot et al., (see pg 397, col 2). Therefore, it would be obvious to one of ordinary skill in the art, with reasonable expectation of success to construct chimeric bacteriorhodopsin/ GPCRs, as taught Popot *et al.* using regions that are structurally analogous between GPCRs and bacteriorhodopsin, as is well established in the art (see Hoflack et al.). The motivation to do so is provided by Popot *et al.* who teach bacteriorhodopsin "can be used as a 'benchtop' on which to arrange engineered loops that are designed to form binding or catalytic sites. Further, the construction of a bacteriorhodopsin chimera at amino acids 171-179 (intracellular loop III) is a matter of routine optimization of operating parameters, as Popot et al. teach that a wealth of data indicates that most of the six loops connecting the transmembrane helices in bacteriorhodopsin can be tampered with to large extents and at least three of them can be cut without preventing refoloding of the proteins (e.g. cytoplasmic loop III, reference 61) (pg 397 col. 2).

11. Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Popot *et al.*, *Current Opinion in Biotechnology* 6:394-402, 1999 and Hoflack *et al., Trends in Pharm. Sci.* 15:7-9, 1994, as applied to claims 1-3, 6-12, in view of Shi *et al., J. Biol. Chem.* 270(5)2112-2119, 1995.

Claims 4 and 5 require the elements of claims 1-3 as discussed above, yet claims 4 and 5 also require that the chimeric construct be capable of catalyzing the GTP-GDP exchange of a G-protein. While Popot et al. disclose that the cytoplasmic loops of bovine rhodopsin (a GPCR) are

tolerant to modification, they do not disclose which region is required for G-protein activation. Shi *et al.* disclose that it is cytoplasmic loop III that is critical to G-protein activation (see page 2119, middle paragraph). Therefore it would be obvious to one of ordinary skill in the art, at the time the invention was made, with reasonable expectation of success, to produce a bacteriorhodopsin/bovine rhodopsin chimera for functional studies of rhodopsin, as taught by Popot et al (e.g. page 397, col. 2) wherein the third cytoplasmic loop of bacteriorhodopsin is substituted for that of bovine rhodopsin because the third cytoplasmic loop of rhodopsin is critical for G-protein activation (as taught by Shi *et al.*). The motivation to do so is provided by Popot *et al.* who teach bacteriorhodopsin "can be used as a 'benchtop' on which to arrange engineered loops that are designed to form binding or catalytic sites.

Conclusion

No Claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

October 19, 2001

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
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